Painful Bladder Syndrome/Interstitial Cystitis and Related Disorders

DEFINITION

PBS (ICS definition):

- "**S/P pain** related to **bladder filling**, accompanied by **other symptoms** such as increased daytime & night time frequency, in the **absence of proven UTI or other obvious pathology**"

➔ "pain/pressure/discomfort" is the primary component of PBS/IC

IC (ICS definition):

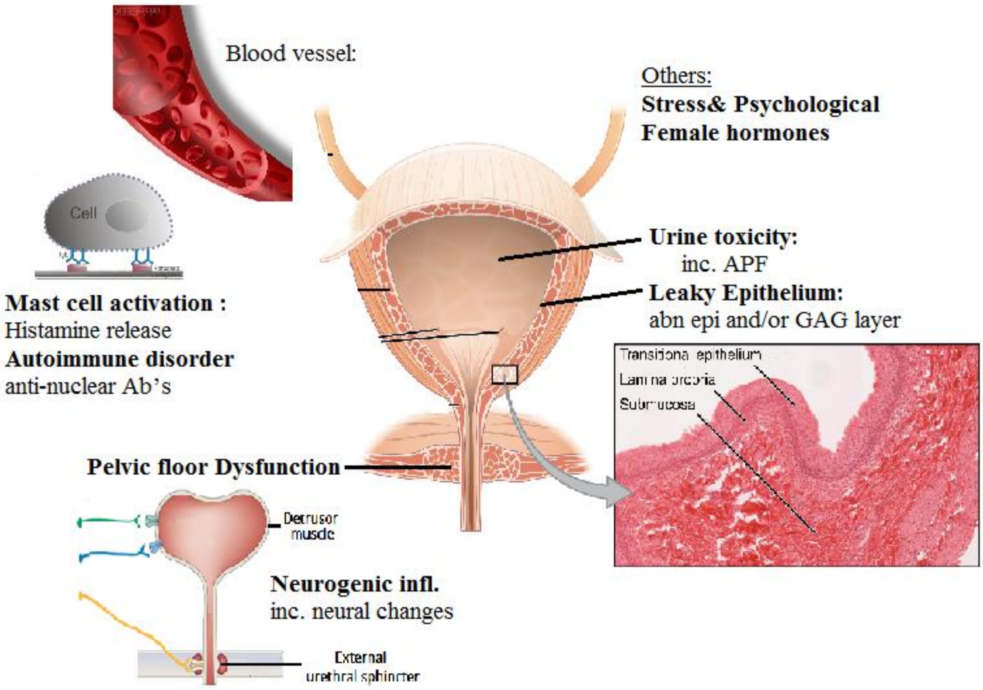
- reserved for patients with "typical cystoscopic & histological features" (undefined).

➔ should be considered part of PBS/IC

EPIDEMIOLOGY

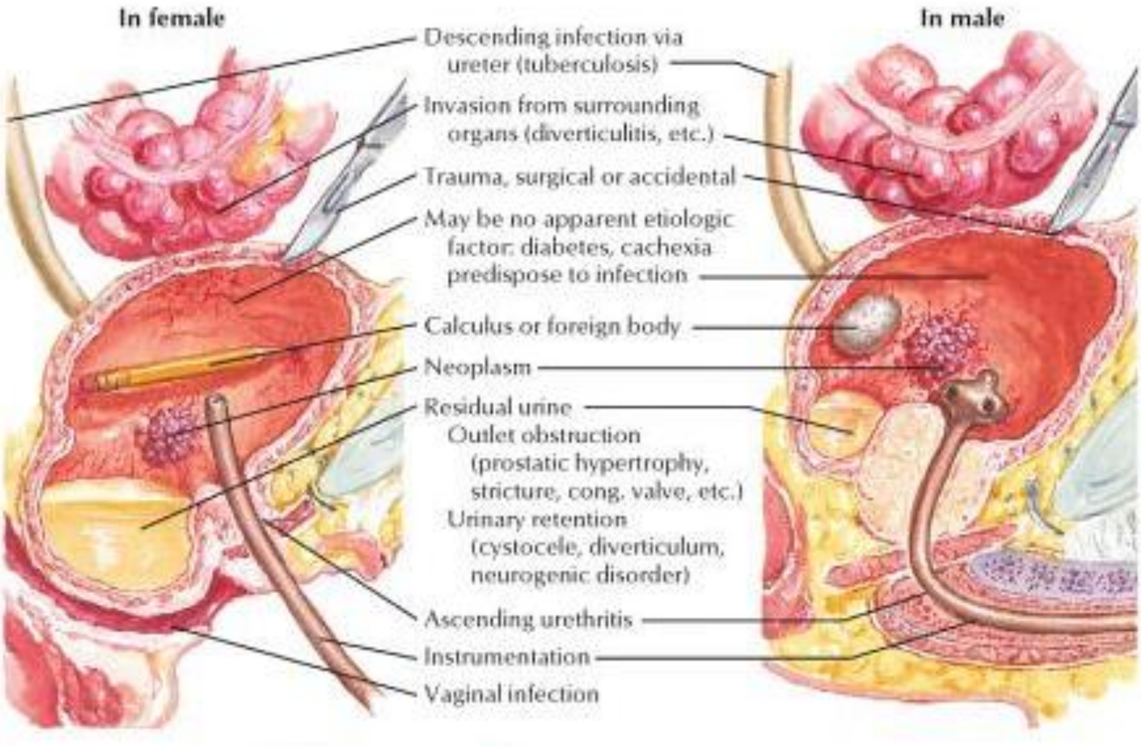
- median age at onset is 40yrs, F:M ratio = 5:1
- ~10% have severe symptoms
- benign condition } not pre-malignant

Etiology: Theories on the cause of PBS/IC: (likely multifactorial)

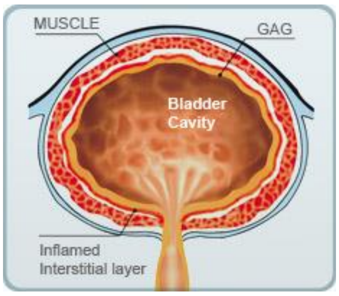


1) Mast cell activation:
    - **histamine release** (a pathognomonic marker)
2) Infection of bladder wall (chronic)
3) Autoimmune disorder
    - anti-nuclear Ab's, response of symptoms to steroids
4) Neurogenic inflammation
    - evidence of increased neural changes in IC
    - may be result of leaky epithelium/GAG + mast cell activation
5) "**Leaky epithelium**": abN epithelium and/or GAG layer
6) Urine toxicity
    - induction of toxic, allergic, or immunologic inflammation
    - increased anti-proliferative factor (APF; a frizzled 8 protein) in IC urine.
7) Others:
    - Stress, estrogen/female hormones, pelvic floor dysfunction, psychologic

Etiology of Cystitis:


In female
In male
Descending infection via ureter (tuberculosis)
Invasion from surrounding organs (diverticulitis, etc.)
Trauma, surgical or accidental
May be no apparent etiologic factor: diabetes, cachexia predispose to infection
Calculus or foreign body
Neoplasm
Residual urine
Outlet obstruction (prostatic hypertrophy, stricture, cong. valve, etc.)
Urinary retention (cystocele, diverticulum, neurogenic disorder)
Ascending urethritis
Instrumentation
Vaginal infection

Pathology



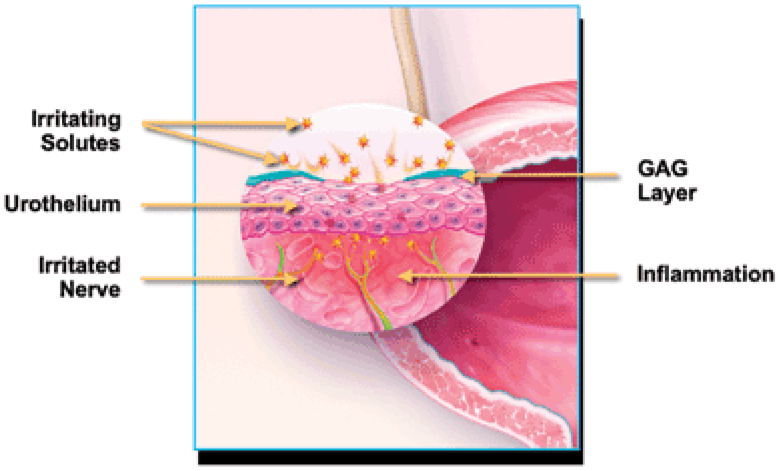
- Classes of GAG layer:
  - hyaluronic acid, heparin sulfate
  - heparin (only one not found on bladder surface).
  - chondroitin 4-sulfate, chondroitin 6-sulfate
  - dermatan sulfate, keratan sulfate.

- Findings on pathology suggest PBS/IC: **(no pathognomonic histology)**
  - normal
  - ulcers (denuded urothelium extending into LP)
  - submucosal inflammation, edema or hemorrhage
  - granulation tissue
  - increased number of activated mast cells (on tryptase stain).

C/P:

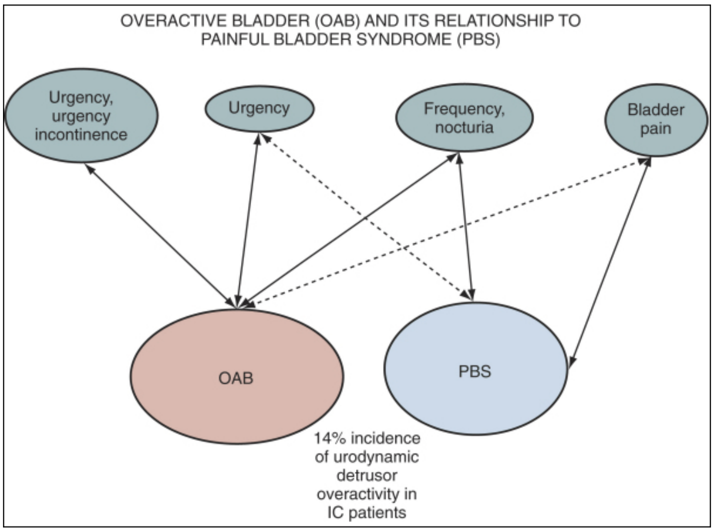
- characteristic clinical features of **non-nociceptive pain**:
  1) out of proportion w/ degree of pathology found (or no pathology found)
  2) noxious stimuli causes pain greater than expected (hyperalgesia)
  3) non-noxious stimuli → pain (allodynia)
  4) extent of pain boundary is greater than expected based on site of original pathology

Mechanism of Pain in PBS



- the 3 main PBS/IC symptom scales:
  1) Univ. of Wisconsin IC Scale
     - 25 total questions with 7 specific PBS/IC questions
  2) O'Leary-Sant IC Symptom Index
     - 4 questions per index specific to PBS/IC and IC Problem Index (urgency, frequency, nocturia, bladder pain)
     - correlates strongly with PBS/IC
  3) Pelvic Pain and Urgency/Frequency (PUF)
     - 8 questions

- symptoms
  - Chronic **pain/pressure/discomfort** associated with the bladder,
  - usually accompanied by urinary **frequency**, in the absence of any identifiable cause


OVERACTIVE BLADDER (OAB) AND ITS RELATIONSHIP TO PAINFUL BLADDER SYNDROME (PBS)
Urgency, urgency incontinence
Urgency
Frequency, nocturia
Bladder pain
OAB
PBS
14% incidence of urodynamic detrusor overactivity in IC patients

Diagnosis

Dx of exclusion

- Conditions ruled out before making the Dx of PBS/IC:

قراءة سريعة

  - Carcinoma (bladder, urethra, prostate, uterus, vagina, vulva, etc)
  - Infections (UTIs, STDs, TB, etc), schistosomiasis and malacoplakia
  - Voiding dysfunction
  - Drug-induced non-bacterial cystitis (eg cyclophosphamides, ASA, NSAIDs, allopurinol, etc)
  - Urethral abnormalities (strictures, diverticulum, etc)
  - Eosinophilic cystitis
  - scleroderma
  - detrusor endometriosis

- **The 1990 NIDDK diagnostic criteria for IC:** (National Institute of Diabetes, Digestive, and Kidney disease):

1) **Either classic Hunner's ulcer or glomerulations** (distention to 80-100 cm H_2O x 1-2mins; present in ≥3 quadrants of bladder with ≥10 glomerulations per quadrant) on cystoscopy AND
2) **Pain** associated with either the bladder OR urinary urgency

N.B:

- glomerulations has low sensitivity and specificity.
- Hunner's ulcer: only present in <5%

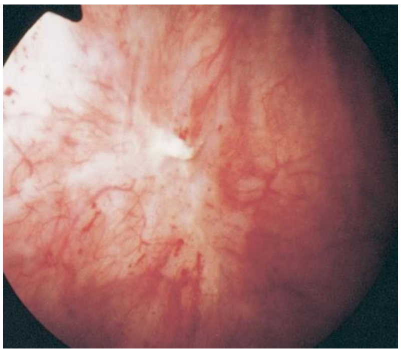
قراءة سريعة

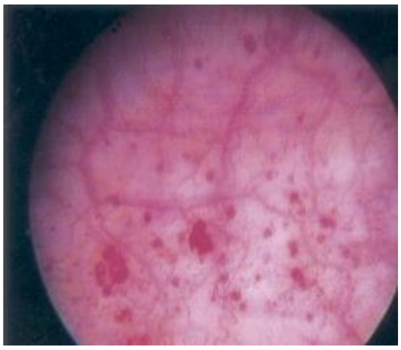
- History
  - bladder pain with urinary frequency & nocturia +/- urgency, relieved by voiding
  - Age >18yrs, duration >6months , incontinence
  - Voiding diary, fluid intake, caffeine intake, bowel habits, sexual hx.
  - associated symptoms: CVA tenderness, N/V, fever, chills, wt loss, night sweats
  - PMHx: stones, UTIs, STDs, GU cancers, chemo (cyclophosphamide), hx of GU TB, RADs, neurogenic bladder (MS, SCI, stroke), urethral strictures, depression, anxiety
  - associated diseases
  - Meds, allergies, smoker, EtOH, drugs, occupational exposure

- Physical Exam
  - general appearance, vitals
  - abdo exam } masses
  - genital exam } ulcers, diverticulum, tumours
  - bimanual in women
  - neurologic } focused exam

- ***Inv***.:
  - **Lab**:
    - urinalysis, urine C&S, urine cytology
    - urinary markers of PBS/IC: all are of debatable clinical utility
      1) **Anti-proliferative factor (APF) levels:**
         - most accurate w/ highest sensitivity & specificity of the various possible markers.
      2) Mast cells, histamine levels, Eosinophilic cationic protein
      3) GAG excretion, NOS levels
    - **Intravesical KCl test: (sensory nerve provocative ability of NS vs KCl (400mEq/L KCl solution)**
      - **Pain and provocation of symptoms = +ve tes**t suspicious for IC.
        - rare to have false +ve's } **good specificity**
        - high false –ve rate } poor sensitivity
      - Indicate abn. "leaky" urothelium or hypersensitive sensory ns.
      - Not diagnostic but may stratify which patients might respond to certain Rx (eg GAG replacement)
      - DDx of a +ve intravesical KCl test:
        - IC/CPPS (men and women)
        - Prostatitis (chronic)
        - UTI, OAB
        - Radiation cystitis
  - **Rad**. mainly to r/o other etiologies
    - U/S
    - CT abdo/pelvis
- Bladder cystoscopy:

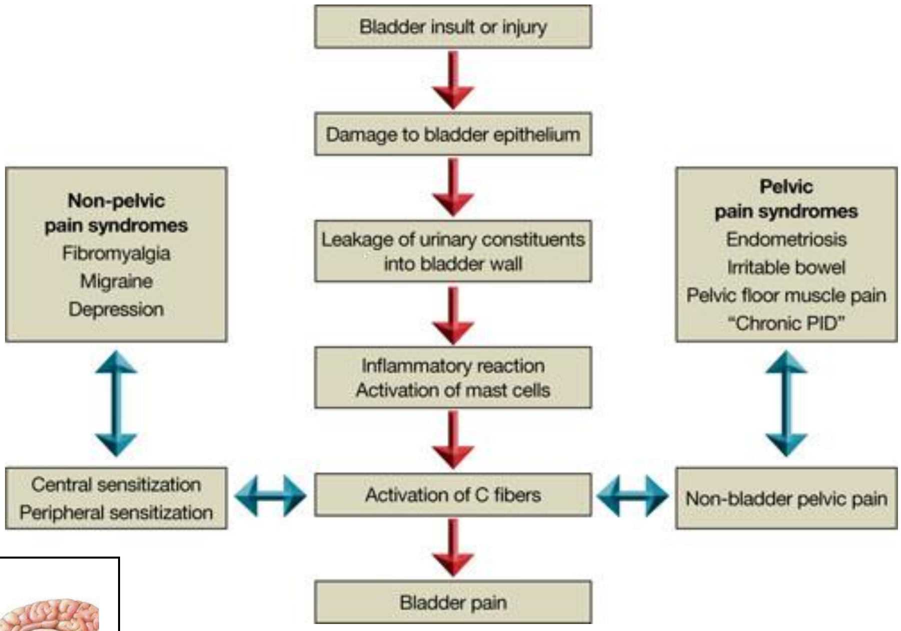
Either classic Hunner's ulcer or glomerulations



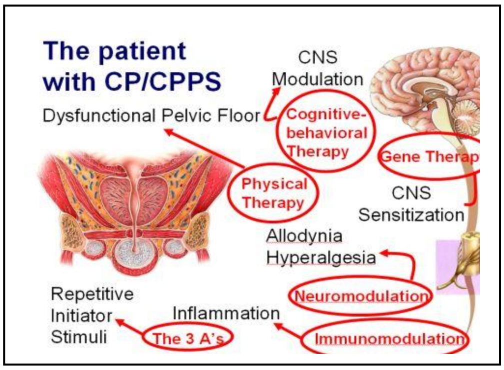


DDx

- Of Bladder Glomerulations:
    - IC/PBS
    - Diversion
    - CIS, Radiation, Toxic chemotherapy/chemicals
    - ESRD with low urine output (dialysis)
- Common conditions associated with PBS/IC:
    - Allergies (MOST COMMON >40%), SLE, Sjogren’s syndrome
    - IBS/IBD
    - Fibromyalgia
    - vulvar vestibulitis/focal vulvitis
- List chronic visceral pain syndromes affect urogenital & rectal areas:
    - PBS/IC
    - vulvodynia
    - orchialgia,
    - penile pain
    - rectal pain



ttt Plan



ttt:

Conservative therapy

NO evidence that early Rx affects the natural hx or course of PBS/IC

1) Watchful waiting/observation: if symptoms are tolerable
2) Education
3) Behaviour modification: helpful in the short-term (voiding diary, timed voiding, controlled fluid intake, stress reduction, exercise)
4) ABx (empiric course) eg doxycycline- If not tried before
5) Dietary changes (caffeine, EtOH, spicy foods, acidic drinks, cheese, citrus fruits, preservatives, etc)
6) PFMT + biofeedback
7) Massage (soft tissues)
8) Acupuncture

Oral therapy

1) **TCAs**
    - Amitriptyline (staple medication for IC) 25 to 100mg po qHS
2) anti-histamines
    - Hydroxyzine (Atarax) } H1-receptor blocker
    - Cimetidine } H2-receptor blocker
3) **Pentosan Polysulfate (PPS)**
    - synthetic heparin analogue (GAG) ie ELMIRON
    - 100 to 300mg po TID (only 3-6% excreted in urine)
4) Analgesics
    - NSAIDs, Opioids,
5) anticonvulsants (Gabapentin, Topiramate)
6) Immunosuppressive
    - steroids, cyclosporine, MTX

7) others:

- no benefit on RCT:
    - nalmefene (opiate antagonist), L-arginine (amino acid), benzydamine (antiinflammatory)
- no RCTs :
    - nifedipine, Quercetin (bioflavonoid), montelukast (anti-leukotriene)

TCAs:

- Mech.
    - central and peripheral anticholinergic actions (at some sites)
    - blocks presynaptic reuptake of serotonin and noradrenaline
    - sedative
    - potent H1-histaminergic receptor blocker
    - stimulate β-adrenergic receptors in bladder smooth muscle
- contraindications to TCA therapy:
    - Cardiac:
        - long QT syndrome
        - significant heart blocks
        - recent MI (within 6/12), unstable angina, CHF, frequent PVCs
        - hx of sustained ventricular arrhythmias
    - orthostatic hypoTN
    - severe liver disease
    - closed-angle glaucoma
- side effects
    - drowsiness/sedation
    - nausea, constipation, dry mouth
    - postural hypoTN
    - decreased libido
    - increased appetite and wt gain
    - arrhythmias

PPS

- Side effects
    - **alopecia** (reversible)
    - GIT: diarrhea, nausea, abdo pain
    - CNS: headache, dizziness
    - skin rash, bleeding problems (rare)
    - may promote breast CA in those at high-risk

Intravesical and intradetrusor therapy

1. Lidocaine mix
2. GAG Analogues:
    a. Pentosan polysulfate (PPS)
        - GAG analogue
        - 300mg in 50cc NS

    b. Heparin
        - GAG analogue + anti-inflammatory effects
        - 10K-40K units instilled
        - no systemic absorption

    c. hyaluronic acid (GAG)

    d. Chondroitin sulfate
3. Dimethyl sulfoxide (DMSO)

    ↓'d mast cell histamine release & desensitizes nociceptive pathways
4. Silver nitrate: **oldest treatment**
    - contraindicated in VUR, recent bladder surgery
5. Intradetrusor Botulinum toxin A: currently being researched
6. others

    - resiniferatoxin (capsaicin anbalogue), BCG
    - Clorpactin WCS-90, oxybutynin

Neural-based treatments

1) TENS (transcutaneous electrical nerve stimulation)
   - relief of pain by stimulating myelinated afferents to activate segmental inhibitory circuits
   - reduce urinary frequency
   - high or low frequency (2-50 Hz)
2) acupunture
   - treatment at Sp. 6 point
3) lumbar epidural blockade
4) neuromodulation
   - direct sacral nerve stimulation (most commonly S3)
   - best results for those with pain + pelvic muscle dysfunction
   - trial stimulation period before implanting permanent neural prosthesis
   - also used for refractory urge incontinence

HYDRODISTENSION

➢ Mech.
- damage to mucosal afferent nerve endings
- under GA ~80cm of H2O for minutes
  - ○ can also look for glomerulations and Hunner's ulcers

➢ Complications
  - ○ risk of perforation or rupture
  - ○ hematuria, low back pain common
  - ○ worsening of symptoms can occur in ~5%

➔ capacity <200cc under GA (rare) predicts failure of medical therapy.

Prognosis:

- ~50% temporary spontaneous remission rate (mean duration ~8 ms)
- hx of childhood bl. problems is 10x more in IC patients vs controls
- hx of UTIs is 2x more common in IC patients

Surgical therapy

➔ option only after all trials of non-surgical rx have failed

1) transurethral resection of Hunner’s ulcers
   - provides symptomatic relief
2) supratrigonal cystectomy + augmentation
   - may need CIC post-op } disaster for IC patients
3) total cystectomy + conduit or neobladder
   - recommended if trigone “affected” by IC
4) diversion
   - may be complicated by pyocystitis, hemorrhage, severe pain, and unremitting spasms and feelings of incomplete emptying
5) historical approaches

- sympathectomy
- intraspinal alcohol injections

N.B: **Refractory PBS/IC**

- failure of oral, intravesical therapy and minimally invasive surgical options (hydrodistension, TUR, fulguration, etc) more aggressive modalities
  - neuromodulation, pain clinic, narcotic analgesics
  - experimental protocols
  - surgical therapy (aug. cystoplasty, urinary diversion +/- cystectomy)

URETHRAL SYNDROME

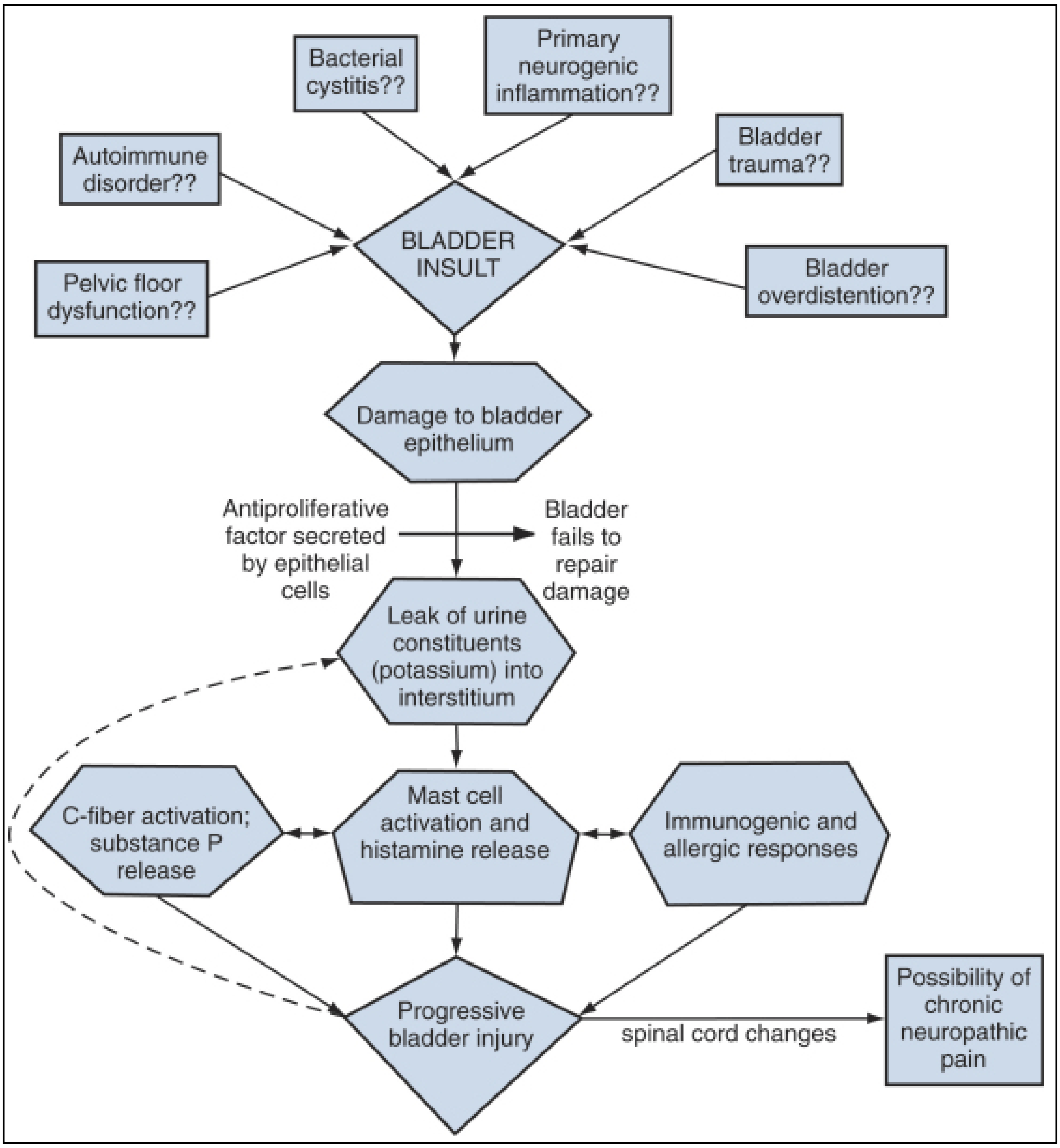
HISTORICAL DIAGNOSIS

- nonspecific constellation of symptoms including frequency, urgency, dysuria, and suprapubic discomfort **with no objective urologic abnormalities**
- acute vs chronic

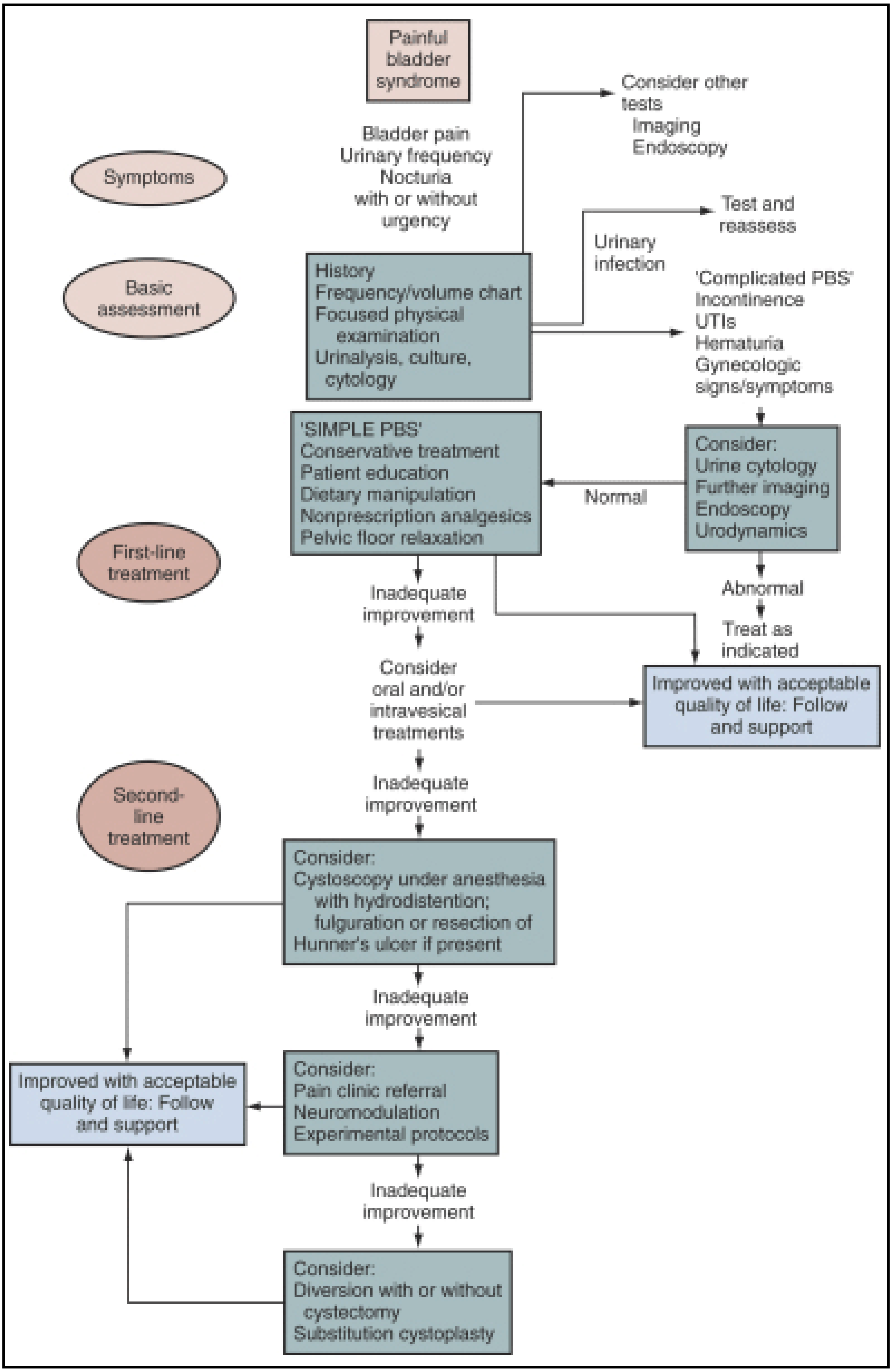
باختصار

PBS

Etiology:


Bacterial cystitis??
Primary neurogenic inflammation??
Autoimmune disorder??
Bladder trauma??
BLADDER INSULT
Pelvic floor dysfunction??
Bladder overdistention??
Damage to bladder epithelium
Antiproliferative factor secreted by epithelial cells
Bladder fails to repair damage
Leak of urine constituents (potassium) into interstitium
C-fiber activation; substance P release
Mast cell activation and histamine release
Immunogenic and allergic responses
Progressive bladder injury
spinal cord changes
Possibility of chronic neuropathic pain

Diagnosis and ttt



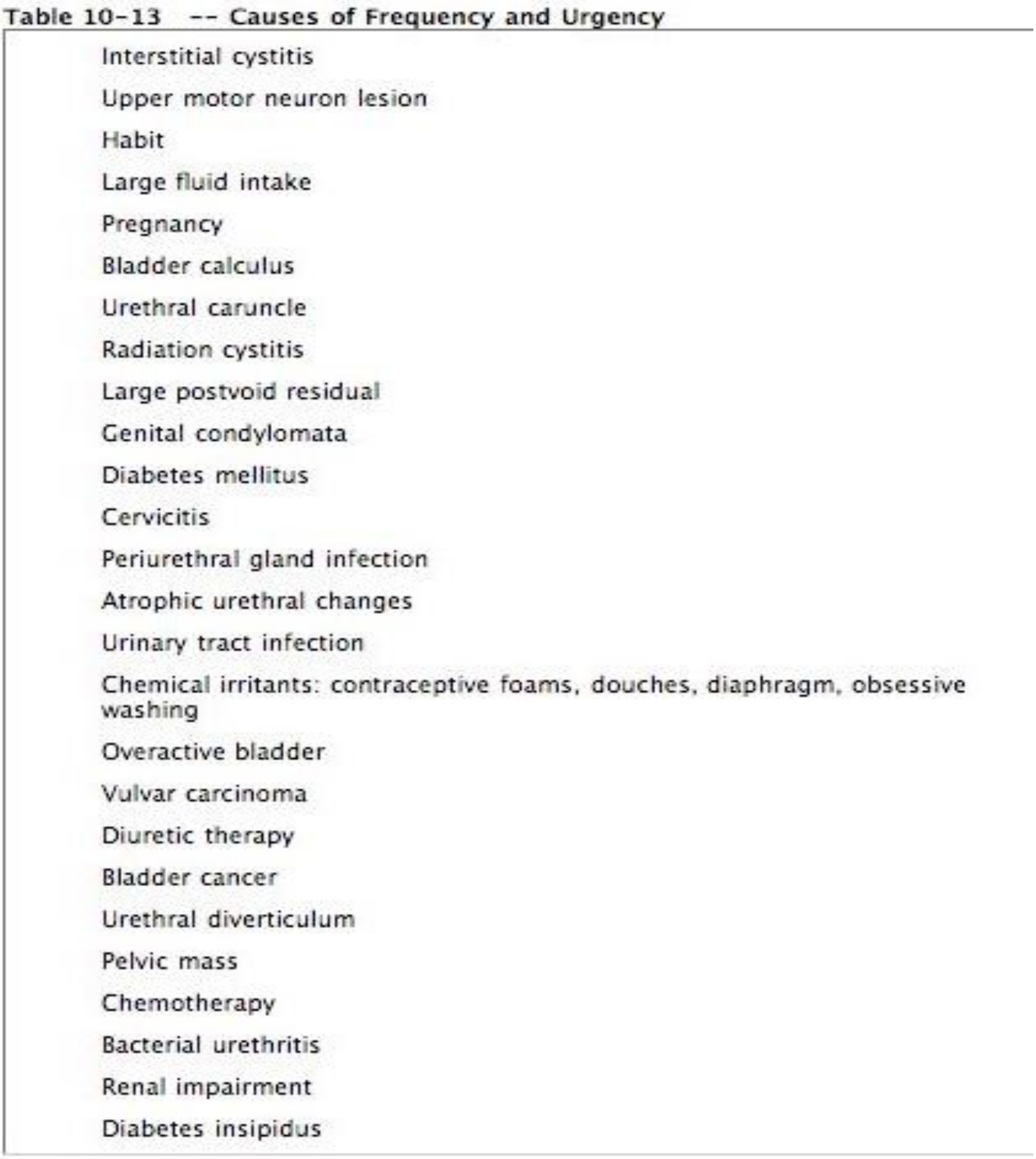


Table 10-13 -- Causes of Frequency and Urgency

- Interstitial cystitis
- Upper motor neuron lesion
- Habit
- Large fluid intake
- Pregnancy
- Bladder calculus
- Urethral caruncle
- Radiation cystitis
- Large postvoid residual
- Genital condylomata
- Diabetes mellitus
- Cervicitis
- Periurethral gland infection
- Atrophic urethral changes
- Urinary tract infection
- Chemical irritants: contraceptive foams, douches, diaphragm, obsessive washing
- Overactive bladder
- Vulvar carcinoma
- Diuretic therapy
- Bladder cancer
- Urethral diverticulum
- Pelvic mass
- Chemotherapy
- Bacterial urethritis
- Renal impairment
- Diabetes insipidus